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MEASUREMENTS OF PASSIVE SMOKING AND ESTIMATES OF LUNG CANCER RISK AMONG NON-SMOKING CHINESE FEMALES

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Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. Relative risks based on the husband's smoking habits, or lifetime estimates of total years, total hours, mean hours/day, or total cigarettes/day smoked by each household smoker did not show dose-response results. Similarly, when such categories as mean hours/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that peripheral tumors in the middle or lower lobes, or, less strongly, squamous or small-cell tumors in the middle or lower lobes, had increasing relative risks that might indicate some association with passive smoking exposure.

Epidemiological data linking passive smoking with lung cancer among non-smokers have been controversial. Six studies (Hirayama, 1981; Trichopoulos *et al.*, 1981; Correa *et al.*, 1983; Knoth *et al.*, 1983; Miller, 1984; Garfinkel *et al.*, 1985) found significantly elevated relative risks (RR) in the range of 2.0 to 3.5 based on the smoking habits of the spouse. Five other studies (Garfinkel, 1981; Kabat and Wynder, 1984; Chan and Fung, 1982; Koo *et al.*, 1984; Wu *et al.*, 1985) two of which were conducted in Hong Kong, did not find significantly elevated RR from inhalation of sidestream tobacco smoke.

Four of these epidemiological studies (Hirayama, 1981; Trichopoulos *et al.*, 1981; Garfinkel, 1981; Chan and Fung, 1982) defined exposure solely by two questions: whether the spouse smoked (yes/no), and the number of cigarettes smoked per day by the spouse. Five other studies (Correa *et al.*, 1983; Miller, 1984; Garfinkel *et al.*, 1985; Kabat and Wynder, 1984; Wu *et al.*, 1985) also included questions about whether involuntary smoke exposure had occurred at work (yes/no), and/or whether the parents has smoked (yes/no). Such data seem rather crude indices of exposure, providing only very indirect information on the degree and amount of exposure. Furthermore, although spouse(s), parents, or co-workers might have smoked, the actual degree of contact of the non-smoker with these smokers could have been very low, or even nil (Friedman *et al.*, 1983). In our detailed studies (Koo *et al.*, 1983, 1984) of passive smoking exposures, smoking parents or spouses were sometimes recalled as inflicting little or no exposure on the subject. In those cases where, for example, the husband smoked but lived separated from the wife, then our study counted such wives as unexposed subjects. Among our never-smoked subjects, this was found to be true for 3 cases and 3 controls.

In order to assess the possible causal relationship of passive smoking to lung cancer risk, data from detailed life-history exposures that were elicited in intensive 1.5- to 2-hr tape-recorded interviews of never-smoked female lung cancer cases and district controls have been analyzed. Emphasis is placed on the consistency of the data, the strengths of the RR, and whether dose-response relationships were present.

This study of the effects of passive smoking is particularly pertinent to Hong Kong because it is one of the most crowded urban environments in the world. Its urban density averages 28,000 inhabitants/km^2, with only 8 m^2 of available living space per person.

MATERIAL AND METHODS

From 1981-3, 88 never-smoked female lung cancer patients and 137 never-smoked female district controls were interviewed as part of a larger retrospective study of female lung cancer in Hong Kong covering 200 cases and 200 controls. In the original study, patients were matched with an equal number of healthy controls by age (±5 years), district of residence (N = 34), and housing type (public or private housing), the latter being an indication of socio-economic status. Details of subject selection, lung cancer histological typing, and method of conducting the interviews have been discussed elsewhere (Koo *et al.*, 1983, 1984). Never-smoked subjects were defined as those who had smoked less than 20 cigarettes in the past. All data on passive smoking exposures were double-checked with other data elicited in the life-history interviews, especially residential patterns since birth (*i.e.* where they lived, type of housing, number of rooms, number of co-habitants, etc.), occupations, and marital life to reduce errors in estimating exposure levels.

Among the never-smoked subjects, the mean age of the patients was 57.8 (SD 10.81) and that for the controls was 59.3 (SD 9.94). This sample included 60 who were widows and 3 who had never married; none had married more than once.

In the design of the interviews, separate data were collected to take into account that within the life-histories of the subjects, sidestream tobacco smoke could originate from: (a) different people who smoked in the presence of the subject; (b) different places frequented by the subject; and (c) different types of tobacco. Persons who smoked included related and unrelated members of the household, and even co-habitants who shared an apartment unit (if their tobacco smoke was noticed by the subject). It was difficult to quantify exposure levels from places that could have varying daily amounts of environmental tobacco smoke and were occasionally visited by the subject such as cinemas, while playing majong, or in transport vehicles. This analysis will only take into account exposures that remained relatively regular during the lifetimes of the subjects *i.e.* from exposures at home and the workplace(s). Among our subjects, tobacco smoke mostly originated from cigarettes smoked by household members, and from pipes (water and regular) smoked by parents or in-laws.

In addition to data based on the husband's smoking habits, 4 other measurements of passive smoking were evaluated: (a) total years of exposure, (b) total hours of exposure, (c) mean hours/day of exposure, and (d) total cigarettes per day smoked by each household member weighed by their years of exposure. These measures should be a more accurate reflection of past lifetime exposures than simple questions based on whether the spouse or parents smoked (yes/no), or whether environmental tobacco smoke was encountered in the workplace (yes/no).

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The total years of exposure were derived from adding the years during which tobacco exposure occurred in the home or workplace. Exposures of 6 or more months were rounded off to the next year. In the home environment, household smokers were only counted if the subject recalled that they had smoked in her presence. Where exposure was concurrent, as in the case of both parents smoking, or exposure occurring at the home and workplace, then the years were not added.

The total hours of exposure were calculated by multiplying the average hours/day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. Each of these sources of exposure was then added together for each subject. The hours were not added for exposure to simultaneous smokers. For example, a husband and son smoking at the same time for 1 hr would only be counted as 1 hr.

The mean hours/day of exposure were derived by adding the hours/day of home and workplace exposures and dividing this figure by the age of the subject. This figure approximates the average number of hours of exposure per day experienced by the subject, spread over her lifetime.

A weighted average of the total cigarettes per day smoked by each household member was calculated from the summation of the usual number of cigarettes smoked throughout the day by each household member multiplied by the years that each lived with the subject, divided by the total years during which cigarette exposure had occurred in the home. This figure may give a better indication of the intensity of cigarette exposure in the home than one simply based on the number of cigarettes smoked per day by the husband, because it accounts for other household smokers and the years that the subject was exposed to each smoker. This figure excluded exposure from pipe smoking and the cigarette consumption levels of co-workers because of difficulties in quantifying those amounts.

Of the 88 patients, 83 were typed histologically. Among the remaining 5 cases, biopsy or cytologic materials revealed that malignant cells were present, but they were too undifferentiated or unspecified for categorization by cell type. Chest radiographs were examined for all cases, and the site of the primary lung tumor was classified by its location in the bronchial tree, and whether it was centrally or peripherally situated. In this analysis, the lingula was classified as equivalent to the middle lobe, and peripheral tumors were defined as those located beyond the segmental bronchus.

Statistical analyses included the calculation of RR as the crude or adjusted odds ratio and tests for trend (Breslow and Day, 1980). Adjusted odds ratios were estimated by the use of a conditional logistic regression package, PECAN, (Lubin, 1981) which was based on N:M matching by strata defined by district (N=34) and housing type (public or private). To take into account the effects of potential confounders which affected the RR estimates, adjustments were made for age (<50, 50-69, 70+), any formal schooling (yes/no), number of live births, and years since exposure to cigarette smoke had ceased in the home or workplace. The exact values were used for the last two variables. Because the resulting large numbers of matching strata in the adjusted odds ratios may lead to unstable results, both crude and adjusted RR were presented for all risk analyses. The Mantel-Haenszel test for trend was performed on all the crude odds ratios using the midpoint of each interval, whereas the trend test of the logistic parameters was based on each variable as a continuous exposure factor.

RESULTS

To allow comparison of the results of this study with those done elsewhere, exposures based on the husband's cigarette smoking habits were analyzed for the ever-married women (Table I). In response to the question of whether the husband had smoked cigarettes in the presence of the wife, the crude and adjusted RR were both a non-significant 1.6. RR for the usual number of cigarettes smoked per day by the husband did not indicate increasing risk with higher smoking levels, and the trend tests for the crude ($p=0.10$) and adjusted ($p=0.43$) RR were not significant.

Likewise, when the data were analyzed in terms of cigarette smoke exposure during childhood/adulthood, or by the number of smoking co-habitants, as in the study of Sandler *et al.* (1985) (Table II), no consistent pattern emerged; RR at the higher levels of exposure, *i.e.*, both childhood and adulthood, or 2+ smoking co-habitants, were found to be lower than those at lower levels of exposure.

Lifetime exposure measurements

When the crude and adjusted odds ratios were calculated for the 4 lifetime exposure measurements, the RR for the intermediate exposure levels of mean hours/day (1.94 and 4.10), and cigarettes/day (1.57 and 2.56) were significant (Table III). However, with the exception of total years, all of the RR (0.9-1.4) at the high exposures were below those of low or intermediate levels. Even for total years, the Mantel-Haenszel linear trend test ($p=0.55$) for the crude RR, and the trend test for the logistic adjusted parameters ($p=0.23$) indicated that the pattern was insignificant.

When the crude and adjusted RR are compared (Fig. 1), the adjusted RR for these measurements showed RR fluctuating between wider ranges of 1.0 to 4.1, yet both lacked evidence of a consistent dose-response pattern.

Intensity

As a measure of intensity, RR were calculated to see whether there was a direct relationship between increasing years and mean hours/day of exposure in a 2×2 table (Table IV). Starting with the top left-hand square which was the group with the lowest exposure levels, one would expect RR to be higher in all the other squares, especially the one at the lower right, because it had the highest years and mean hours/day of exposure. However, the crude RR at this highest intensity level was only 1.07, and the category with the lowest intensity values (top left) had the highest adjusted RR of any of the other groups. A similar pattern emerged if total hours or cigarettes/day were substituted for mean hours in this analysis.

Age of initial exposure

We had previously found no difference in the age at which passive exposure had started (Koo *et al.*, 1984). To see whether earlier age of initial exposure combined with higher years of exposure were related with increasing risk, RR were calculated for cigarette exposures in a 2×2 table (Table V). Again, we did not see any pattern suggesting a dose-response relationship. The top left square with the least years of exposure and older age at initial exposure had the highest crude and adjusted RR. Similar results were obtained if the years and age of exposure included all types of environmental tobacco smoke, *i.e.* from cigarettes and pipe.

Histological type

The cases were divided into two groups, those with squamous or small-cell lung tumors, and those with adenocarcinoma or large-cell lung tumors. This division was made because the former group was previously found in Hong Kong to be more related to active smoking than the latter (Koo *et al.*, 1985). Five cases with mixed cell types and 5 with unspecified cell types were excluded from the analysis.

Although none of the crude or adjusted RR or trends by histology were found to be significant, it can be observed that a dose-response pattern seemed to be more apparent among

TABLE I - HUSBAND'S CIGARETTE SMOKING HABITS AND RR FOR LUNG CANCER AMONG EVER-MARRIED WOMEN

Exposure	Number of cases/ number of controls	Crude RR (95% CI)	Adjusted RR[1] (95% CI)
Husband ever smoked?[2]			
No	35/70	1.00	1.00
Yes	51/66	1.55 (0.94, 3.08)	1.64 (0.87, 3.09)
Cigarettes/day smoked by husband			
0	32/67	1.00	1.00
1-10	17/15	2.37 (1.03, 5.91)	2.33 (0.92, 5.92)
11-20	25/35	1.50 (0.87, 3.64)	1.74 (0.81, 3.75)
21+	12/19	1.32 (0.45, 2.63)	1.19 (0.46, 3.03)

[1]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.-[2]Husband smoked in the presence of the wife. 3 cases and 3 controls were not exposed to the cigarettes of their husband.

TABLE II - RR FOR LUNG CANCER FROM HOUSEHOLD EXPOSURE TO CIGARETTE SMOKE

Exposure	Number of cases/ number of controls	Crude RR[1] (95% CI)	Adjusted RR[2] (95% CI)
By period in life			
No exposure	27/49	1.00	1.00
Children only[3]	2/3	1.21 (—)	2.07 (0.51, 95.17)
Adulthood only[4]	57/77	1.34 (0.84, 3.01)	1.68 (0.62, 5.45)
Both childhood + adulthood	2/8	0.45 (0.11, 3.32)	0.64 (0.57, 5.85)
By number of smoking co-habitants[5]			
None	27/49	1.00	1.00
1	48/68	1.28 (0.82, 3.25)	1.73 (0.57, 6.35)
2+	13/20	1.18 (0.57, 3.65)	1.35 (0.64, 5.03)

[1]Crude odds ratio.-[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.-[3]From one or both parents.-[4]From spouse, in-laws, children, or other co-habitants.-[5] From spouse, parents, in-laws, children, or other co-habitants who smoked at home in the presence of the subject.

TABLE III - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER

Total years				Hours/day			
Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)	Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)
0	22/40	1.00	1.00	0	22/40	1.00	1.00
1-19	20/28	1.30 (0.63, 3.68)	1.95 (0.72, 5.31)	<1	15/29	0.94 (0.41, 2.63)	1.05 (0.37, 2.94)
20-34	24/39	1.12 (0.59, 3.06)	1.36 (0.55, 3.36)	<2	33/31	1.94 (1.24, 6.74)	4.10 (1.59, 10.61)
35+	22/30	1.33 (0.79, 4.44)	2.26 (0.90, 5.67)	2+	18/37	0.88 (0.42, 2.42)	1.00 (0.39, 2.58)
Total hours (in hundreds)				**Cigarettes/day[3]**			
Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)	Exposure	Cases/ controls	RR[1] (95% CI)	RR[2] (95% CI)
0	22/40	1.00	1.00	0	25/48	1.00	1.00
1-10	25/38	1.20 (0.60, 3.67)	1.68 (0.64, 4.45)	1-10	13/16	1.56 (0.74, 4.96)	1.83 (0.65, 5.11)
101-200	23/27	1.55 (0.88, 5.53)	2.28 (0.91, 5.72)	11-20	27/33	1.57 (1.00, 4.99)	2.56 (1.06, 6.19)
201+	18/32	1.02 (0.54, 3.47)	1.42 (0.56, 3.62)	21+	23/40	1.10 (0.51, 2.47)	1.21 (0.51, 2.86)

[1]Crude odds ratio.-[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.-[3]The sum of number of cigarettes/day smoked by each household member weighted by the years of exposure from that source. Mantel-Haenszel trend analysis. Years: 0.55, hours: 0.75, hours/day: 0.70, cig/day: 0.67. Logistic adjusted trend analysis. Years: 0.23, hours: 0.98, hours/day: 0.86, cig/day: 0.63.

TABLE IV - EFFECTS OF INCREASING YEARS AND MEAN HOURS/DAY OF TOBACCO EXPOSURE

	Years of exposure			
	1-24		25+	
Mean hours per day of exposure	RR[1]	RR[2]	RR[1]	RR[2]
<1.5	1.33[3]	2.22[4] (19/26)[5]	1.47	2.13 (21/26)
≥1.5	1.02	1.21 (9/16)	1.07	1.45 (17/29)

[1]Crude odds ratio.-[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.-[3]95% CI: 1.33 (0.68, 4.00), 1.47 (0.74, 4.30), 1.02 (0.39, 3.45), 1.07 (0.57, 3.39).-[4]95% CI: 2.22 (0.79, 6.21), 2.13 (0.84, 5.43), 1.21 (0.37, 3.96), 1.45 (0.56, 3.78).-[5]Number of cases/number of controls. 22 cases and 40 controls had no exposure = RR 1.00.

TABLE V - EFFECTS OF INCREASING YEARS AND EARLIER AGE OF INITIAL EXPOSURE TO CIGARETTE SMOKE

	Years of exposure			
	1-24		25+	
Age at first exposure	RR[1]	RR[2]	RR[1]	RR[2]
≥25	1.50[3]	1.95[4] (20/25)[5]	1.50	1.67 (8/10)
≤24	1.00	1.35 (8/15)	1.25	1.86 (28/42)

[1]Crude odds ratio.-[2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.-[3]95% CI: 1.50 (0.71, 3.99), 1.50 (0.47, 4.64), 1.00 (0.41, 3.42), 1.25 (0.76, 3.60).-[4]95% CI: 1.95 (0.76, 4.98), 1.67 (0.52, 5.33), 1.35 (0.30, 6.18), 1.86 (0.78, 4.46).-[5]Number of cases/number of controls. 24 cases and 45 controls had no exposure = RR 1.00.

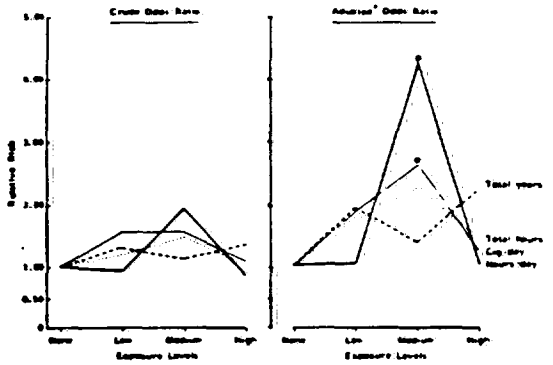

FIGURE 1 - Measurements for passive smoking and RR for lung cancer. [a]Adjusted for age, number of live births, schooling (+/−) and years since exposure to cigarette smoke ceased in the home or workplace. *$p \leq 0.05$.

the squamous or small-cell lung tumors than among the adenocarcinoma or large-cell types (Table VI). This was especially true for the adjusted RR in the former group, as 3 of the 4 measurements consistently indicated increasing risk with increasing exposure.

Location by lobe

Eighty of the cases had the main tumor residing in one of the lobes. The remaining 8 cases, with primary tumors in the right or left main bronchus, or in the right intermedius region, were too few for analysis. Calculations of the RR showed that none of the crude or adjusted values were significant for upper-lobe tumors (Table VII). For the middle or lower lobes, all of the adjusted RR were in the comparatively higher range of 1.9-3.5 for those with some passive exposure. Moreover, for 3 of the exposure measurements, total years, hours/day, and cigarettes/day, the confidence intervals for the crude and adjusted RR indicated some borderline significant values. However, none of the trend analyses for the lobe data came out significant.

TABLE VI - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER BY HISTOLOGICAL TYPE

	Squamous or small-cell			Adenocarcinoma or large-cell		
	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years						
0	7/40	1.00	1.00	12/40	1.00	1.00
1-26	10/46	1.24 (0.37, 5.40)	1.58 (0.37, 6.77)	17/46	2.11 (0.54, 3.74)	2.07 (0.64, 6.71)
27+	15/51	1.68 (0.47, 5.79)	1.82 (0.49, 6.80)	17/51	1.90 (0.51, 3.27)	1.43 (0.51, 4.02)
Total hours (in hundreds)						
0	7/40	1.00	1.00	12/40	1.00	1.00
1-150	12/56	1.22 (0.34, 4.71)	1.40 (0.34, 5.77)	18/56	1.07 (0.48, 3.05)	1.70 (0.55, 5.20)
151+	13/41	1.81 (0.52, 6.54)	2.04 (0.53, 7.85)	16/41	1.30 (0.59, 4.02)	1.57 (0.55, 4.49)
Hours/day						
0	7/40	1.00	1.00	12/40	1.00	1.00
<1.3	8/44	1.04 (0.31, 4.70)	1.34 (0.31, 5.84)	17/44	1.29 (0.56, 3.61)	2.19 (0.71, 6.77)
≥1.3	17/53	1.83 (0.52, 6.69)	2.01 (0.52, 7.72)	17/53	1.07 (0.49, 3.23)	1.34 (0.47, 3.82)
Cigarettes/day						
0	9/48	1.00	1.00	13/48	1.00	1.00
1-19	9/26	1.85 (0.57, 7.20)	2.02 (0.53, 7.68)	12/26	1.70 (0.77, 5.72)	2.05 (0.63, 6.72)
20+	14/62	1.20 (0.36, 3.31)	1.19 (0.36, 3.93)	19/62	1.13 (0.59, 3.57)	1.88 (0.68, 5.17)

[1]Crude odds ratio - [2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.

TABLE VII - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER BY LOBAR LOCATION

	Upper lobes			Middle or lower lobes		
	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years						
0	10/40	1.00	1.00	11/40	1.00	1.00
1-26	11/46	0.96 (0.43, 3.82)	0.98 (0.27, 3.64)	17/46	1.34 (0.86, 8.72)	3.08 (0.83, 11.38)
27+	16/51	1.25 (0.40, 2.87)	1.42 (0.46, 4.42)	15/51	1.07 (0.62, 6.15)	2.13 (0.62, 7.24)
Total hours (in hundreds)						
0	10/40	1.00	1.00	11/40	1.00	1.00
1-150	15/56	1.07 (0.30, 2.38)	1.30 (0.38, 4.50)	18/56	1.17 (0.76, 7.26)	2.37 (0.67, 8.35)
151+	12/41	1.17 (0.38, 3.01)	1.23 (0.39, 3.91)	14/41	1.24 (0.68, 7.17)	2.51 (0.72, 8.84)
Hours/day						
0	10/40	1.00	1.00	11/40	1.00	1.00
<1.3	7/44	0.64 (0.15, 1.58)	0.69 (0.18, 2.61)	17/44	1.40 (0.95, 9.51)	3.24 (0.90, 11.66)
≥1.3	20/53	1.51 (0.51, 3.70)	1.64 (0.54, 5.01)	15/53	1.03 (0.55, 5.55)	1.97 (0.57, 6.82)
Cigarettes/day						
0	10/48	1.00	1.00	12/48	1.00	1.00
1-19	10/26	1.85 (0.57, 5.39)	2.32 (0.62, 8.76)	12/26	1.85 (1.08, 10.39)	3.49 (0.98, 12.50)
20+	17/62	1.32 (0.48, 3.32)	1.79 (0.59, 5.45)	17/62	1.10 (0.61, 4.61)	1.93 (0.63, 5.95)

[1]Crude odds ratio - [2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.

Proximal/peripheral location

Among the 85 determinable cases, 46 had peripheral tumors, and 39 proximal tumors. Although only the crude RR of 2.00 and adjusted RR of 3.52 for 1-19 cigarettes/day were slightly significant for the proximal tumors, in general, all of the crude and adjusted RR for the peripheral tumors were greater than 1.00 (Table VIII).

Histological type and location

In order to see whether any particular combination of histological type, lobe, or proximal/peripheral location of the tumor would result in stronger dose-response patterns by the 4 lifetime measurements of passive smoking, RR were analyzed for the 12 possible 1:1 combinations. We were unable to segregate the cases into any finer categories than 2 of the 3 groups because of the small resulting number of cases for analysis. Space does not allow us to present all the tables, but the best combination was that of peripheral tumors in the middle or lower lobes (Table IX). Among the RR, significant or nearly significant figures were found for the crude or adjusted RR relating to at least one of the exposure categories for each type of measurement. Moreover, the adjusted RR tended to range between the relatively high values of 6.5 to 18.7 for those with some exposure (Fig. 2), and most of these were significant or nearly significant. None of the trend tests came out significant, but this and the tendency for the higher levels of exposure to have lower RR than the low levels of exposure may have been due to the small number of cases (N=24).

Although not as apparent, squamous and small-cell lung cancers in the middle or lower lobes (Fig. 3) also seemed to show some positive association with passive smoking. There were only 18 cases with this type for analysis and none of the RR or tests for trend were found to be statistically significant (Table X). Yet it was promising to see that all the RR with some exposure were greater than 1.0. Among the highest exposure levels for the adjusted RR, values as high as 7.0 were found for total hours, and 6.2 for hours/day.

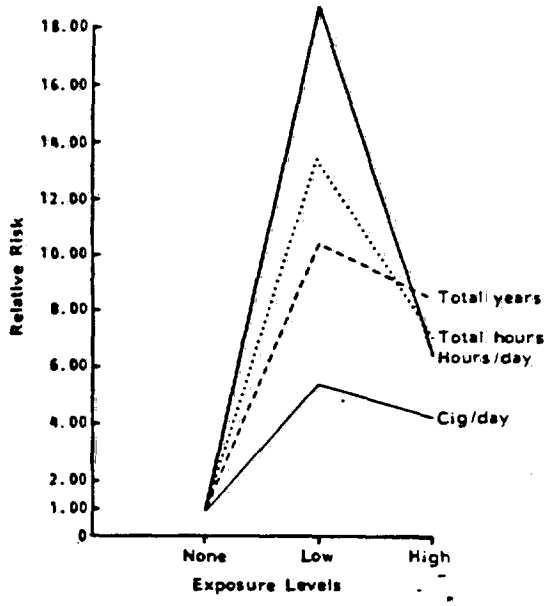

FIGURE 2 - Measurements of passive smoking and RR for peripheral lung cancers in the middle or lower lobes. Adjusted odds ratio.

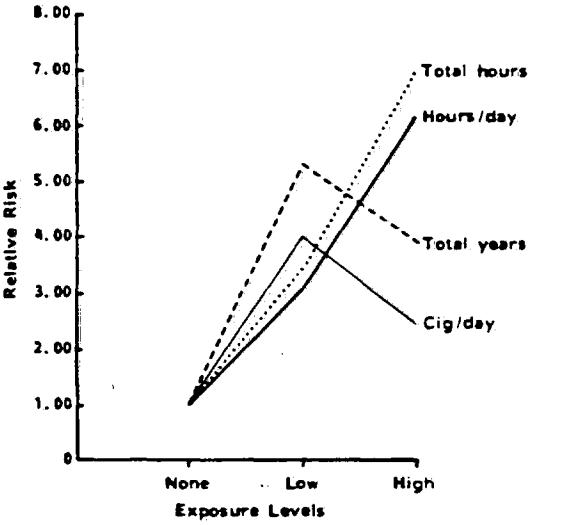

FIGURE 3 - Measurements of passive smoking and RR for squamous and small-cell lung cancer in the middle or lower lobes. Adjusted odds ratio.

DISCUSSION

For comparative purposes, the more commonly used measurements of passive smoking based on yes/no questions of whether household co-habitants (husband, childhood/adulthood, or others) had smoked, or on the number of cigarettes the husband smoked per day, were presented. Only the crude RR of 2.37 (95% CI:1.03-5.91) for husbands smoking 1-10 cigarettes/day was of borderline significance and none of the adjusted odds ratios were significant at the $\leq 5\%$ probability level. There was little indication that increasing levels of such exposure led to increased RR.

On the basis of our extensive life-history data, we were able to calculate the total years, hours, mean hours/day, and cigarettes/day to which the subjects had been exposed to tobacco smoke at home or at work. Our estimates were based on the understanding that the household composition of each subject would change as she progressed through the life-cycle of birth, childhood, adulthood, marriage, motherhood and, for 27%, widowhood. We also included exposures from each workplace at which the subject had worked for at least 3 months. In our adjusted RR, the effect of cessation of exposure to passive smoking was accounted for by putting in the years that exposure had ceased at home and/or workplace as a continuous regressor variable.

Despite such detailed accounting, we were unable to find a significant trend in the crude or adjusted RR for these 4 lifetime measurements of passive smoking. Although the RR for the intermediate level exposures of hours/day and cigarettes/day were significant, the RR at the highest levels of exposure for these two variables fell to a non-significant 1.0-1.2. In fact, the RR for the highest exposure levels for 3 out of the 4 measurements were below all of those with lower exposures, and ranged from a very weak 1.0 to 1.4. On the other hand, most of the crude and adjusted RR were greater than 1.00.

TABLE VIII - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR LUNG CANCER BY LOCATION OF TUMOR

	Peripheral			Proximal		
	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years						
0	10/40	1.00	1.00	11/40	1.00	1.00
1-26	18/46	1.57 (0.59, 4.84)	1.52 (0.44, 5.17)	14/46	1.11 (0.50, 4.14)	2.15 (0.64, 7.19)
27+	18/51	1.41 (0.64, 4.78)	1.84 (0.62, 5.45)	14/51	1.00 (0.43, 3.51)	1.58 (0.51, 4.92)
Total hours (in hundreds)						
0	10/40	1.00	1.00	11/40	1.00	1.00
1-150	20/56	1.43 (0.63, 4.97)	1.82 (0.57, 5.85)	16/56	1.04 (0.46, 3.53)	1.86 (0.58, 5.97)
151+	16/41	1.56 (0.60, 4.71)	1.66 (0.54, 5.06)	12/41	1.06 (0.47, 4.19)	1.72 (0.54, 5.51)
Hours/day						
0	10/40	1.00	1.00	11/40	1.00	1.00
<1.3	14/44	1.27 (0.56, 4.62)	1.66 (0.52, 5.33)	13/44	1.07 (0.48, 3.94)	2.21 (0.63, 7.75)
≥1.3	22/53	1.66 (0.66, 4.98)	1.77 (0.59, 5.32)	15/53	0.89 (0.44, 3.69)	1.59 (0.51, 4.93)
Cigarettes/day						
0	12/48	1.00	1.00	12/48	1.00	1.00
1-19	11/26	1.69 (0.73, 6.14)	1.91 (0.57, 6.35)	13/26	2.00 (0.98, 9.17)	3.52 (1.01, 12.27)
20+	23/62	1.48 (0.70, 4.34)	1.79 (0.64, 5.03)	12/62	0.77 (0.34, 2.45)	1.23 (0.42, 3.62)

[1]Crude odds ratio - [2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.

TABLE IX - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR PERIPHERAL LUNG CANCERS IN THE MIDDLE OR LOWER LOBES

Exposure	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years			
0	4/40	1.00	1.00
1-26	10/46	2.17 (0.98, 84.95)	10.44 (0.91, 119.53)
27+	10/51	1.96 (0.88, 66.91)	8.61 (0.84, 88.21)
Total hours (in hundreds)			
0	4/40	1.00	1.00
1-150	12/56	2.14 (1.24, 110.17)	13.51 (1.16, 157.74)
151+	8/41	1.95 (0.69, 56.35)	7.02 (0.64, 76.93)
Hours/day			
0	4/40	1.00	1.00
<1.3	11/44	2.50 (1.71, 160.18)	18.70 (1.53, 228.03)
≥1.3	9/53	1.70 (0.62, 49.89)	6.49 (0.60, 70.37)
Cigarettes/day			
0	6/48	1.00	1.00
1-19	6/26	1.85 (0.95, 24.36)	5.53 (0.79, 38.86)
20+	12/62	1.55 (0.74, 13.14)	4.16 (0.77, 22.55)

[1]Crude odds ratio - [2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.
Mantel-Haenszel trend analysis: Years: 0.15, hours: 0.16, hours/day: 0.14, cig/day: 0.29.
Logistic adjusted trend analysis: Years: 0.15, hours: 0.66, hours/day: 0.53, cig/day: 0.22.

TABLE X - MEASUREMENTS OF PASSIVE SMOKING AND RR FOR SQUAMOUS AND SMALL-CELL LUNG CANCERS IN THE MIDDLE OR LOWER LOBES

Exposure	Number of cases/ number of controls	RR[1] (95% CI)	RR[2] (95% CI)
Total years			
0	3/40	1.00	1.00
1-26	7/46	2.03 (0.52, 44.44)	5.29 (0.51, 54.71)
27+	8/51	2.09 (0.42, 33.01)	3.97 (0.41, 38.22)
Total hours (in hundreds)			
0	3/40	1.00	1.00
1-150	6/56	1.43 (0.35, 29.32)	3.44 (0.35, 34.17)
151+	9/41	2.93 (0.59, 46.98)	7.01 (0.64, 76.60)
Hours/day			
0	3/40	1.00	1.00
<1.3	4/44	1.21 (0.30, 29.64)	3.05 (0.28, 33.14)
≥1.3	11/53	2.77 (0.57, 44.05)	6.16 (0.59, 64.48)
Cigarettes/day			
0	4/48	1.00	1.00
1-19	5/26	2.31 (0.58, 23.25)	3.97 (0.54, 29.20)
20+	9/62	1.74 (0.44, 11.87)	2.58 (0.42, 15.93)

[1]Crude odds ratio - [2]Adjusted for age, number of live births, schooling (+/−), and years since exposure to cigarette smoke ceased in the home or workplace.
Mantel-Haenszel trend analysis: Years: 0.23, hours: 0.20, hours/day: 0.26, cig/day: 0.20.
Logistic adjusted trend analysis: Years: 0.71, hours: 0.76, hours/day: 0.70, cig/day: 0.78.

Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cigarettes/day) by mean hours/day of exposure, also did not indicate a dose-response relationship. Likewise, the analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher RR. It was troubling to find that in both types of analysis, the RR for the lowest amounts of exposure were among the highest values.

Dalhamn *et al.* (1968) noted from their study of the retention of cigarette smoke components in human lung, that water-insoluble volatile compounds and particulate matter from cigarettes tended to be deposited primarily in the deeper parts of the respiratory tree. Since adenocarcinoma is predominant among non-smoker lung cancer cases (59% of our typed cases) and it is generally a peripheral tumor, we wanted to see whether the passive smoking measurements would exhibit a more consistent pattern among the adenocarcinoma and large-cell types, and/or among the peripheral tumors. In general, the peripheral tumors as a group showed stronger dose-response results than the adenocarcinomas.

The RR for total years, hours, and hours/day measurements of squamous and small-cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted RR for adenocarcinoma or large-cell lung cancers. This association of histology with passive smoking is also suggested from previous studies by Trichopoulos *et al.* (1981) and Correa *et al.* (1983).

Analysis of the cases by the lobe location of the tumor was done to see whether the primary tumor resided more frequently in the upper lobes than in the lower lobes. This is because it is known that when dust is inhaled, it first enters the upper lobes where much of it is deposited, and then travels down to the lower lobes (Time, 1980). Furthermore, it has been observed (J.H-C. Ho, personal observation) that up to half of the Hong Kong adult population have radiologically evident scars on the upper lobes of their lungs. Most of these scars are due to previous tuberculosis infection. Since "lung cancer is more common in the scarred and chronically diseased lung" (Stone *et al.*, 1978), we were interested to see whether the lobe data would substantiate any of these possibilities. In fact, 37 of the lung cancers were found in the upper lobes, and 43 in the middle or lower lobes. The results from the RR estimates from the 4 types of measurements did not show the upper lobes to be more sensitive to environmental tobacco smoke.

Wynder and Goodman (1983) suggested that lung cancer in non-smokers was more likely to occur in the periphery of the lung. This was found in our study, as 54% of the determinable cases had peripheral tumors *vs.* 46% with proximal tumors. Moreover, the pattern of RR with the various measurements of passive smoking indicated that peripheral tumors seemed to exhibit better dose-response RR than proximal tumors.

When the RR were calculated for the 12 possible 1:1 combinations resulting from histological type, location by lobe, or proximal/peripheral tumors, the highest RR were found for peripheral tumors in the middle or lower lobes. Significant adjusted RR as high as 18.7 were found for some of these measurements. Although RR at the lower doses tended to be higher than that for the higher doses, the data were consistent in that all the RR for those with some exposure were much greater than 1.0, and the adjusted RR for at least one of the RR for each type of measurement was statistically significant or nearly significant.

The RR analysis for squamous and small-cell lung cancers in the middle or lower lobes also appeared somewhat better than the others, with total hours and hours/day measurements showing some dose-response pattern. With the above two combined analyses showing some promise, perhaps the best RR would have been obtained if analysis had been done with squamous or small-cell peripheral tumors in the middle or lower lobes. We were unable to do these calculations because only 8 cases fitted into this category.

Actually, the finding of a possible risk of squamous and small-cell tumors in the middle or lower lobes was somewhat unexpected, given that dust particles tend to adhere to the upper lobes, and tuberculosis usually affects the upper lobes. To see whether calcified foci or fibrosis in the upper lobes could account for the higher RR in the middle or lower lobes because the previous presence of such lesions might disturb the expected distribution of inhaled particulate or gaseous matter, most of the chest radiographs of cases with squamous and small-cell lung tumors were re-examined. No significant difference was found in the proportion of positive cases with upper lobe *vs.* lower lobe tumors.

In our analysis of *all* never-smoked cases, the lack of a dose-response pattern, and an almost consistent drop in the RR at the highest doses of exposure would seem to lend little, or only weak support for the passive smoking linkage with lung cancer for women in Hong Kong. This might be due to the fact that it has been estimated (Rylander *et al.*, 1983) that the non-smoker exposed to environmental tobacco smoke receives about 1% of the active smoker's dose of tobacco smoke based on cotinine levels in the body, and this is roughly equivalent to the tobacco smoke of 0.1-1.0 cigarette inhaled by an active smoker in a day. Moreover, a 15- to 17-year longitudinal study of 97 non-smoking females in Holland did not find an association between passive smoking exposure and pulmonary function decline (Brunekreef *et al.*, 1985). Thus the effects of passive smoking might be so weak that they are easily overshadowed by other environmental factors such as diet or exposure to inhaled gaseous/particulate matter from other sources in the home or the workplace.

When the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small-cell tumors in the same lobes, exhibited better RR patterns for passive smoking in terms of consistency, strength, and dose-response. We are not sure whether this proclivity for passive-smoking-related lung tumors to reside in the middle or lower lobes might be due to the fact that the lower lobes have more bronchial cells at risk than the upper lobes, or whether the size, weight, or composition of gaseous or particulate matter from passive smoking may favor its adherence to the peripheral areas and the lower lobes. Nevertheless, the overall proportion of lung tumors in the middle or lower lobes among our 88 cases ranged from 27% for the peripheral tumors to 20% for the squamous or small-cell tumors. Thus, the majority of lung cancers among our non-smoking population were probably due to some factor(s) which yet remain to be identified.

The results from this study, showing a weak effect of passive smoking on the risk of lung cancer among never-smoked Hong Kong Chinese women, must be interpreted cautiously, since it was based on only 88 cases and 137 controls. With this sample size, RR less than approximately 1.4 would be difficult to detect with 95% power and at the 5% level of significance. This problem was even greater when the cases were stratified by histological type and location of the primary tumor. However, these data seem consistent with the findings from other epidemiological, biochemical, and physiological studies in showing higher risks for squamous-cell tumors in the peripheral areas of the lung. Confirmation of these findings from other studies is therefore needed.

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